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ON THE USE OF STRYCHNIN IN BROKEN CARDIAC COMPENSATION.[1]

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Many English and American clinicians are in the habit of prescribing strychnin for persons suffering from acute and chronic heart failure. Strychnin is used for this purpose because it is believed that it increases the work of the heart and that it slows and steadies the pulse. Yet an unbiased examination of the evidence will show that there is no sound basis for this belief. Pharmacologists have not been able to demonstrate that strychnin increases the output from the heart. Clinicians have not shown that broken cardiac compensation can be relieved by strychnin. But since physicians continue to employ strychnin in the treatment of heart disease despite these facts, it is important to furnish data about which there can be no reasonable doubt. Such data, to be absolutely convincing, must be quantitative. One may measure the effect of a drug on broken cardiac compensation by recording the rate of the pulse, the rate of the respiration, the weight, the fluid intake, and the urinary output, before, during, and after its administration.

Earlier Studies. *Pharmacological Observations.* Igersheimer,[2] in 1905, reviewed the work of earlier observers and added important new data. It is to be noted that the pharmacologists always used amounts of strychnin which were many times the therapeutic dose—amounts which invariably caused convulsions. For example, in two instances, Igersheimer gave rabbits 0.055 gram and 0.375 gram. For men of average weight this would mean 3 grams and 12 grams. It is not safe or reasonable to assume that effects obtained with such large quantities would also follow therapeutic doses. But even if we do assume that such effects would be produced by amounts which may safely be given to patients, there is nothing in the pharmacological data which would lead us to believe that strychnin is indicated in the treatment of heart disease.

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[1] Aided by a grant from the Council on Pharmacy and Chemistry of the American Medical Association.

[2] Ueber die Wirkung des Strychnins auf das Kalt und Warmblüherherz, Arch. f. exp. Path. u. Pharm., 1905, liv, 73.

An examination of the literature shows that the earlier observations made on the hearts of warm-blooded animals are conflicting. Sometimes a slight acceleration, at other times a slight slowing, was noted. Igersheimer carefully studied the action of strychnin on the isolated and intact rabbits' heart. He could produce no change in rate until he had injected several times the amount which would cause convulsions in non-curarized animals. As the dose was gradually increased the heart beats became less frequent and weaker and the blood-pressure fell.

In 1911 Cameron[3] published his observations on the effect of strychnin on the heart. His technique was so elaborate that it is difficult if not impossible to analyze his results. He, however, sums up his work thus: "Strychnin in large or small doses tends to increase cardiac tonicity, except when the slowing is too great or when the slowing is associated with increased blood-pressure or when the increase in blood-pressure alone is sufficient to counteract the tendency to increased tonicity." A drug which can increase tonus only under such ideal conditions can have but little value in the treatment of heart disease even if the increased tonus is desirable. But is the type of increased tone said to be caused by strychnin ever advantageous if, as Cameron himself points out, it is accompanied by a decrease in systolic output?

It is apparent that the laboratory studies of the action of strychnin show that doses permissible in man can be of no direct use in the treatment of heart disease.

Let us now turn to the evidence gathered by clinical observers.

Clinical Observations. James Mackenzie,[4] speaking of "cardiac tonics," has written the following about strychnin, "the most popular remedy of this class is strychnin. I have carefully sought for its special effect on the heart and found none. When I inquired into the evidence for its supposed good effect I found that it was practically all clinical, and clinical evidence endows the drug with the most diverse properties. It is recommended as a cardiac stimulant in slow acting hearts, and even in heart-block it is said to quicken the beat. It is also recommended in the too excitable heart, as when there are extrasystoles, and in the rapid heart of acute myocardial affections. It is said to be beneficial in cases of low blood-pressure and equally beneficial in the cases of high tension and even in angina pectoris. The evidence that can show a drug to possess the property of exciting the sluggish and of soothing the excited, of raising the low pressure and of relieving the high, speaks more for unreasoning faith in the drug than for the beneficial properties of the drug itself."

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[3] Johns Hopkins Hosp. Rep., 1911, xvi, 549.

[4] Diseases of the Heart, London, 1908, p.267.

In the studies of Parkinson and Rowlands[5] the observations were made in such a manner that any immediate effect of strychnin when given subcutaneously in severe heart failure would be recorded quantitatively. The data were collected from fifty cases after they had been in the wards three to eight hours. The rate and character of the pulse and the rate of respiration were recorded with the Mackenzie polygraph, and the systolic blood-pressure with a Leonard Hill sphygmomanometer. Readings were made ten minutes, five minutes, and just before the injection of one-fifteenth grain of strychnin, and every five minutes for one hour after the injection. The work was controlled by giving the last ten patients an injection of water instead of strychnin. The following results were obtained:

On no occasion was any increase in blood-pressure produced. The average slowing of the pulse after the injection of strychnin was 3.3 beats per minute. The slowing which followed the injection of water was somewhat greater. There was no effect on the irregularity of the pulse. Neither the rate nor the amplitude of respiration were changed. There was no objective improvement in any case. These data fully warrant the conclusion which Parkinson and Rowlands reach, namely, that "strychnin has no effect which justifies its employment as a rapid cardiac stimulant in cases of heart failure."

The evidence which shows that a single dose of strychnin does not benefit persons suffering from heart failure does not prove that the prolonged use of the drug may not be a material aid in the relief of broken cardiac compensation. We have accordingly investigated the possible effect of the administration of large doses of strychnin over a period of several days in persons suffering from chronic heart failure.

PROLONGED USE OF STRYCHNIN. *Method.* The cases were studied in accordance with the following plan: The patients upon entrance to the ward were placed on a diet of liquids and soft solids and the liquids were limited to 1000 c.c. in the twenty-four hours. If there was sufficient dyspnea or cough to prevent sleep, morphin or codein was ordered. The bowels were moved with various cathartics. The weight was noted. The temperature, pulse, and respirations were recorded twice daily. The twenty-four-hour fluid intake and urinary output were noted. The patients were kept in bed throughout the period of observation. For the first few days after entrance the clinical course of the affection was watched. Many patients will entirely recover their compensation as a result of this *regime* without the aid of digitalis. It is important to exclude all such cases from a series in which the effect of any given drug upon the heart is to be studied. Only those patients who showed no persistent slowing of the cardiac or respiratory rates, no increased output of urine and no loss of weight after three or four days, were considered unimproved. Failure to observe this precaution may cause an error of as much as 50 per cent. The patients who did not recover their compensation were then given strychnin, and the effect upon the pulse, respiration, urinary output, systolic and diastolic pressures, weight, and subjective symptoms noted. Finally, digitalis bodies and diuretics were given in order that the effect of strychnin might be compared in the same patient under otherwise uniform conditions, with the effect of remedies whose efficiency is established beyond doubt.

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[5] Strychnin in Heart Failure, Quart. Jour. Med., 1913, vii, 42.

Strychnin was studied in this way in eight cases of broken cardiac compensation. Table I shows the total dose of strychnin, the size of the individual doses, and the period of time over which the drug was given to each patient. Further details will be found in the accompanying case histories and charts.

TABLE I.

Case No.	Total amount of strychnin administered.	Duration of strychnin period in days.	Mode of administration of strychnin.	Remarks.
1	0.3 grain	3	0.03 grain three times a day.	
2	0.4 grain	4	0.03 grain three times a day.	
3	1.4 grain	3	0.1 grain every three hours on the first day; every two hours on the second day; every hour on the third day.	Finally omitted because of toxic symptoms.
4	2.0 grain	3	0.1 grain every two hours when awake.	Finally omitted because of toxic symptoms.
5	0.2 grain	1	0.1 grain at 9 A.M. and 5 P.M.	Discontinued because patient was growing steadily worse.
6	0.3 grain	1	0.1 grain every three hours.	Discontinued because patient was growing steadily worse.
7	1.6 grain	5	0.1 grain every six hours.	
8	0.3 grain	3	0.03 grain three times a day.	

EXPLANATION OF CHARTS.

CHART I.

Case II. A. P. Q., aged sixty years. Arteriosclerosis; weak heart; broken cardiac compensation; dyspnea; right hydrothorax; ascites; edema of legs; continuous irregularity of the pulse, many beats not reaching the wrist. After being in the hospital four days without improvement, he was started on strychnin sulphate, gr. $\frac{1}{30}$, s.c., three times a day. The blood-pressure, taken at short intervals following the first dose, showed no change. After four days of strychnin there was no slowing of the pulse or decrease in its irregularity. The temperature remained subnormal. There was no change in either systolic or diastolic blood-pressure; no diuresis; no subjective improvement. There was an increase in weight. Strychnin was discontinued, and digipuratum given. Gratifying improvement in all the signs noted as unimproved during the strychnin period, followed. The decrease in the irregularity of the pulse was striking.

CHART II.

Case III. A. C., aged thirty years. Mitral stenosis; broken cardiac compensation; dyspnea; continuous extreme irregularity of the pulse; ascites; edema of the ankles. The patient had been in this condition for some time and she made no improvement for the first three days in the hospital. She was started on strychnin on the fourth day. It was omitted at the end of three days, because the patient showed physiological effects at that time. During this period she had been given a total of one and two-fifths grains of strychnin. She, however, made no improvement. There was no slowing of the pulse, no loss of weight, no diuresis, no subjective betterment. On the seventh day she was started on digipuratum. Thereafter she made a steady and satisfactory improvement. The increase in the loudness of the pulmonic second sound was striking. Blood-pressures were not charted on account of the extreme irregularity of the pulse.

CHART III.

Case IV. M. K., aged fifty-five years. Arteriosclerosis; chronic nephritis; broken cardiac compensation; dyspnea; attacks of cardiac asthma; enlarged liver; edema of the legs. After being in the hospital four days without showing any improvement he was started on strychnin sulphate, gr. $\frac{1}{14}$, s.c. On the first day after having been given 0.7 grain of strychnin, he was "jumpy" and felt excited. The strychnin was omitted. The next day 0.7 grain was given. On the third day the patient had 0.6 grain; and the drug was finally omitted that evening because the patient twitched every time he was touched. During the first "strychnin day" he had an attack of acute dyspnea, during which the systolic pressure went up to 300 mm. Hg. As will be seen by the chart, there was no change during the strychnin period. Digipuratum was then started and resulted in rapid marked objective and subjective improvement.

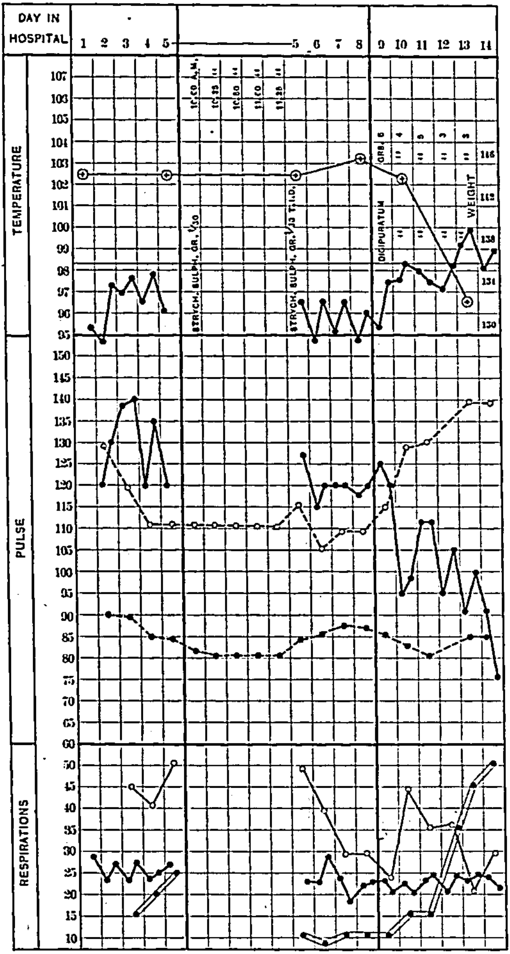
DAY IN HOSPITAL
1 2 3 4 5
5 6 7 8 9 10 11 12 13 14
TEMPERATURE
107 106 105 104 103 102 101 100 99 98 97 96 95
PULSE
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60
RESPIRATIONS
50 45 40 35 30 25 20 15 10
10.00 A.M.
10.35 "
10.50 "
11.00 "
11.25 "
STRYCH. SULPH. GR. 1/30
STRYCH. SULPH. GR. 1/30 T.I.D.
DIGIPURATUM GRS. 6
" 4
" 3
" 3
" 3
WEIGHT
146
142
138
134
130

Chart I.

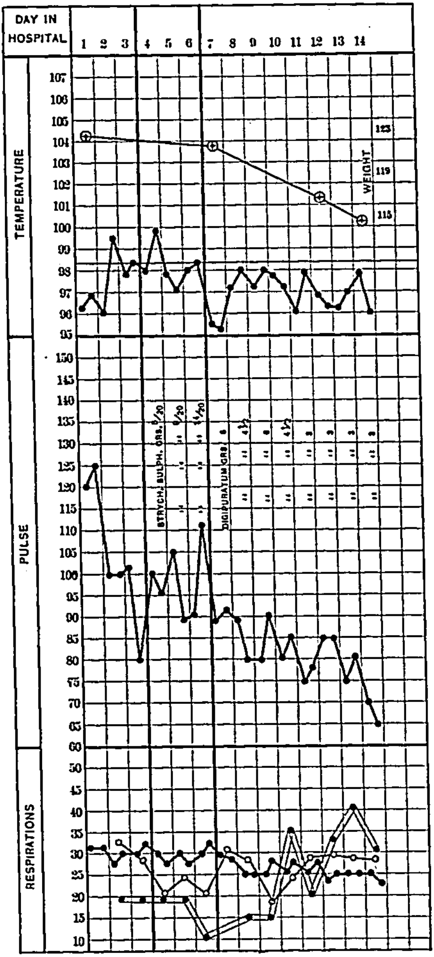
DAY IN HOSPITAL
1 2 3 4 5 6 7 8 9 10 11 12 13 14
TEMPERATURE
107
106
105
104
103
102
101
100
99
98
97
96
95
WEIGHT
123
119
115
PULSE
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
STRYCH. SULPH. GRS. 6/20
" " " 9/20
" " " 11/20
DIGIPURATUM GRS. 6
" " 4½
" " 6
" " 4½
" " 3
" " 3
" " 3
" " 3
RESPIRATIONS
50
45
40
35
30
25
20
15
10

CHART II.

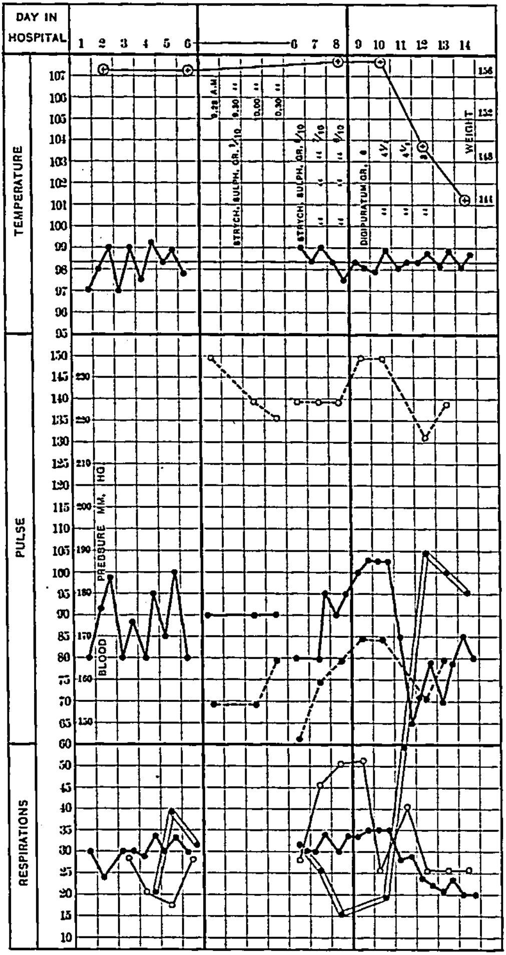
DAY IN HOSPITAL
1 2 3 4 5 6
6 7 8
9 10 11 12 13 14
TEMPERATURE
107 106 105 104 103 102 101 100 99 98 97 96 95
9.28 A.M
9.30 ''
10.00 ''
10.30 ''
STRYCH. SULPH. GR. 1/10
STRYCH. SULPH. GR. 6/10
'' '' 7/10
'' '' 8/10
DIGIPURATUM GR. 6
'' 4½
'' 4½
'' 3
WEIGHT
156 152 148 144
PULSE
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60
BLOOD PRESSURE MM. HG
230 220 210 200 190 180 170 160 150
RESPIRATIONS
50 45 40 35 30 25 20 15 10

CHART III.

CASE HISTORIES. CASE I.—M. V., aged twenty-seven years. Aortic regurgitation; mitral regurgitation; broken compensation; dyspnea; right hydrothorax; ascites; edema of legs. After being in the hospital four days without improvement he was started on strychnin sulphate, gr. $\frac{1}{30}$, s.c., three times a day. After three days there was no slowing of the pulse, no change in the blood-pressure, no diuresis, and no subjective improvement. There was, however, an increase in weight. Strychnin was discontinued and diuretin and digipuratum given. The patient made no improvement, and died twenty days after entering the hospital.

CASE II.—See history accompanying Chart No. I.[6]

CASE III.—See history accompanying Chart No. II.

CASE IV.—See history accompanying Chart No. III.

CASE V.—M. A., aged fifty years. Obesity (weight, 232 pounds); broken cardiac compensation; hydrothorax; ascites; general edema; rapid, feeble pulse. After being in the wards three days he had lost no weight; his dyspnea had increased and his heart sounds had become weaker. The urinary output had fallen. During the previous twenty-four hours he had shown marked Cheyne-Stokes breathing. For the past few hours the periods of apnea were becoming longer. The systolic blood-pressure was about 110 mm. The diastolic pressure could not be determined by the auscultatory method. On the fourth day the patient was given strychnin, gr. $\frac{1}{10}$ s.c., at 9 A.M., and 5 P.M. During the day his breathing became so much worse and his general condition so much poorer that vigorous treatment was indicated. The strychnin was accordingly omitted and camphor, grs. 3, s.c., each two hours, given. The next morning there was gratifying improvement. The patient was then started on digipuratum and diuretin. His compensation was quickly and completely restored.

CASE VI.—M. L., aged thirty-six years. Mitral disease; very severe break in compensation; general anasarca; right hydrothorax and ascites. On the fourth day after entrance the following note was made: "Since entrance the pulse has become progressively more rapid—at first hard to feel it is now almost imperceptible. The systolic blood-pressure is estimated with much difficulty at about 130 mm. The diastolic pressure cannot be obtained by the auscultatory method. In view of the fact that the patient is certainly worse than at entrance, she is started on strychnin sulphate, gr. $\frac{1}{10}$, s.c., each three hours. At 4 P.M., after three doses of strychnin, the patient seemed worse and her condition was such that it was deemed unfair to withhold digitalis any longer. Strychnin was omitted and she was given strophanthin, gm. 0.001, intravenously, and camphor, gr. $1\frac{1}{6}$ s.c., each two hours." The next day she was started on digipuratum, and caffein was substituted for camphor. None of these procedures caused any significant change in the patient's condition. She continued to fail and died several days later.

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[6] The temperature, pulse, and respiration, are represented in the usual way.
The weight is represented thus ⊕——⊕
The fluid intake thus O——O
The twenty-four-hour urinary output thus ●══●
The systolic blood-pressure thus O----O
The diastolic blood-pressure thus ●----●
The dosage and the time of administration of the drug is printed on the chart.

CASE VII.—L. M. A., aged fifty-three years. General arteriosclerosis: auricular fibrillation; myocardial degeneration; broken cardiac compensation; general edema; hydrothorax; ascites. The blood-pressure was not recorded because the irregularity of the pulse prevented its accurate measurement. Repeated estimations, however, showed that it was neither abnormally high nor low. The patient improved very slightly if at all under the routine treatment, which lasted for the first twenty days in the hospital. This was followed by a strychnin period of six days, during which time she was also having digitalis to the point of toxicity. It will be noted that the addition of the strychnin did not make the digitalis any more efficient than it had been during a previous period, when it had also been given to toxicity. The administration of the strychnin resulted in neither a subjective nor an objective improvement. $1\frac{6}{10}$ grains of strychnin were given in four days.

CASE VIII.—E. P. T., aged sixteen years. Chronic endocarditis; mitral and aortic disease; adherent pericardium; hydrothorax; ascites; enlarged liver; general anasarca; gradual failure to death. After having been in the wards for several months, during which time he continued to fail in spite of a variety of therapeutic procedures, he was put on strychnin sulphate, gr. $\frac{1}{30}$, s.c., three times a day. During this period all digitalis preparations were omitted. At the end of three days there was no change in any of the objective signs, and certainly no subjective improvement. Strychnin was accordingly discontinued and routine treatment reinstated. The patient continued to fail, and died several weeks later.

RESULTS. None of the patients were benefited by strychnin. The compensation was not improved in the slightest by the drug. Four patients subsequently recovered their compensation as the result of digitalis administration. Two patients died in the hospital. The other two were discharged unimproved. The failure of strychnin to have its reputed effect cannot be explained by assuming that the patients under observation were beyond all therapeutic aid, because, as was pointed out above, half of them did regain cardiac compensation when given digitalis. These four patients did not recover during the strychnin period solely because strychnin does not improve the work of the heart.

CONCLUSIONS. Neither pharmacological nor clinical evidence justifies the use of strychnin in the treatment of acute or chronic heart failure.